Office Action Summary

Application No.	Applicant(s)
09/707,468	Nocolaides
Examiner	**Art Unit**
Dave Nguyen	1632

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *10/17/02 and 11/22/02*.

2a) X This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1, 2, 4-23, and 25-80* is/are pending in the application.

4a) Of the above, claim(s) *5-8, 12-21, 26-28, and 30-72* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1, 2, 4, 9-11, 22, 23, 25, 29, and 73-80* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16
4) ☐ Interview Summary (PTO-413) Paper No(s).
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

Claims 1, 22, 23, 25 have been amended, claims 3 and 24 have been canceled, claims 73-80 have been added by the amendment filed October, 25, 2002.

The specification has been amend by the supplemental amendment filed November 22, 2002.

Applicant's election with traverse of Group I claims, claims 1-4, 9-11, 22-25, and 29) in the response filed April 16, 2002 is acknowledged.

Claims 5-8, 12-21, 26-28, and 30-72 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 1, 2, 4, 9-11, 22, 23, 25, 29, 73-80, readable on the elected claimed invention are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 9-11, 22, 23, 25, 29, 73-80, readable on a genus of polynucleotide sequences of **a dominant negative allele** of a PMS2 mismatch repair gene, which includes a subgenus of animal and/or mammalian genes coding for any dominant negative allele of any PMS2 mismatch repair gene, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In addition, the claims readable on any *in vivo* method of making a mammalian cell in an *in vivo* environment, *e.g.*, in a **hypermutant transgenic animal including those of humans,** said animal comprising a cell whose genome in which

any generic gene of dominant negative allele of a mismatch repair gene has been introduced are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The application and presently pending claims contemplate that any dominant negative allele of a PMS2 mismatch repair (MMR) gene can be obtained from the cells of humans, animals, yeast, bacterial, or other organisms by screening assays (page 9) and/or by synthetic assays. The as-filed application further contemplates that these polynucleotide sequences can be used to create any colony of hypermutable cultured and recombinant cells. The as-filed application coupled with the cited prior art provides sufficient description of homologs or native cDNA sequences, *e.g.*, SEQ ID NOS: 6, 8, 10, 12, and 14, belonging to a respective subgenus of mouse PMS2, human PMS2, human PMS1, human MSH2, and human MLH1. The as-filed application also incorporates a number of prior art, which mainly discloses that disruption of any native MMR gene including human PMS2 or murine PMS2 cause tumor and/or cancer. However and with respect to a genus of allelic variants of PMS2 MMR genes, which are deemed essential for the intended use of the claimed invention, and which must exhibit the property of being dominant negative, *e.g.*, functional and being dominant over a wild-typed PMS2 MMR genes so as to cause hypermutation in a cell transfected with any variant of PMS2 MMR gene, the application coupled with the cited prior art only provides description the human *hPMS2-134,* which carries a truncation mutation at codon 134, and encodes a dominant negative function over that of wild-typed hPMS2. However, neither the application nor the incorporated references provide structural description of a representative number of species of animal and/or mammalian native cDNA coding for allelic dominant negative PMS2 genes. The claimed invention encompasses an enormous number of nucleic acid sequences encoding dominant negative PMS2 MMR products. The man feature of the claimed invention is the requirement of the availability of a representative number of species of "dominant negative allele of a PMS2 MMR gene". However, Applicant's disclosure of a truncated murine PMS2 and/or human PMS2, and/or potential biological assays to identify other allelic dominant negative PMS2 genes, which are not necessarily sharing any common structure of the disclosed

truncated murine PMS2 and/or human PMS2, does not provide sufficient description of the structures of a representative number of dominant negative PMS2 MMR genes, which would support applicant's possession of the genus of claimed DNA sequences coding for dominant negative PMS2 MMR gene products at the time the invention was made. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, *e.g.* a genus dominant negative allele of a PMS2 MMR gene including those naturally occurring dominant negative alleles, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for isolating the variants; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of such claimed genus of any animal dominant negative MMR genes. A disclosure of no more than a group or subgenus of a dominant negative allele of a PMS2 MMR gene, which allele consists of nucleotide residues coding for the first 133 amino acids of a PMS2 MMR gene product, as in the instant case, is simply a wish to know the identity of any or all DNA sequences encoding any other naturally occurring dominant negative allele of any PMS2 gene. The state of the art exemplified by Ngo *et al.* discloses that a nucleic acid sequence encoding a particular protein determines the protein' s structural, and functional properties, and a biological function of a encoded protein based on the primary amino acid sequence of the protein requires a knowledge of and description with regard to which amino acids in the protein' s sequence and/or nucleotides in the DNA, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which a protein' s structure relates to its functional usefulness (Ngo *et al.*, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.*, (ed.), Birkhauser, Boston, MA, pp. 492-495).

In addition and with respect to claims readable on any *in vivo* transgenic clone and/or methods of making such cells, since differences in expression among lines of animals are caused by "position effect", and since host cell sequences at the site of integration can modify the regulation of the transgene both qualitatively and quantitatively, position effects where the transgene is influenced by its site of integration in the host chromosome can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the

transgene (Polejaeva *et al.* (Theriogenology. Vol. 53. pages 117-126, 2000). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent how one skilled in the art envisions a genus of *in vivo* cells that have no specific phenotype recited in the claims on the basis of applicant's specification. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all DNA and/or dominant negative PMS2 genes, and/or transgenic clones associated with any phenotype, which are broadly defined by the as-filed application, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the claimed dominant negative allele of any PMS2 MMR gene other than the truncated human or mouse PMS2 MMR, which consists of the first 133 amino acids of the respective PMS2 MMR and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Thus, it is not apparent to one skilled in the art as to how claims encompassing a genus "dominant negative allele of a PMS2 MMR" genes and/or

any *in vivo* cell as embraced by the claimed methods and products, find an adequate support from this instant disclosure at the time the invention was made.

Applicant's response (pages 3-5, filed Oct. 17, 2002) has been considered by the examiner but is not found persuasive for the reasons of record. More specifically, Applicant mainly asserts that by disclosing a truncation mutant, *PMS2-134*, and assays and/or methods for identifying other potential dominant negative alleles which are yet to be discovered or disclosed by the as-filed specification, applicant meets the written description requirement, applicant's assertion is not found persuasive because given the breadth of the claims, and the reasons set forth in the rejection, and the disclosure of only one single species of the truncation mutant, *PMS2-134,* the written description requirement was not met, and a skilled artisan would not have recognized that applicants was in possession of the genus of PMS2-dominant negative alleles other than the *PMS2-134*. Applicant further asserts that the claims are not directed to unknown or undisclosed dominant negative forms of *PMS2* genes themselves, but rather to the use of dominant negative forms of *PMS2* genes. In response, the examiner maintains that in order to operate or practice the invention as claimed, a skilled artisan would necessarily have to rely upon the disclosure of a representative number of species of dominant negative forms of *PMS2* genes themselves which is the essential materials required in the claimed methods, and as such, by disclosing just one single species of the truncation mutant, *PMS2-134,* and providing the structural information of the human or murine wild-typed *PMS2,* applicant does not in compliance with the written description requirement.

Claims 1, 2, 4, 9-11, 22, 23, 25, 29, 73-80, are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to:

1/ A method for making a hypermutable, antibody producing cell *in vitro*, comprising introducing into an isolated cell capable of producing antibodies a polynucleotide comprising a dominant negative allele of a *PMS2* mismatch repair gene (MMR), whereby said cell becomes hypermutable and is capable of

producing antibodies, and wherein the dominant negative allele of a *PMS2* mismatch repair gene encodes a truncated PMS2 MMR which consists of the first 133 amino acids coded by said PMS2 MMR gene.

2/ A homogenous culture of isolated hypermutable, antibody producing cells as described in 1/.

The specification is not enabling for claims directed to any other claimed embodiment within the elected claimed invention. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention as broadly claimed so that it would operate as intended by the disclosed as-filed application.

In addition, The specification coupled with knowledge in the prior art does not provide sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention readable on any transgenic clone, without any undue experimentation, particularly on the basis of applicant's disclosure.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As the first issue, while the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce a transgenic animal that exhibit a desired phenotype, regardless whether a gene targeted modification technique rather than a traditional introduction of a desired exogenous protein encoded construct into embryonic cells. Applicants contemplates that by targeting any DNA vector construct encoding any dominant negative allele of MRR gene via homologous recombination into an endogenous genomic site containing the endogenous and native MMR gene of any animal cell including animal pluripotent, animal embryo-derived stem (ES) cells, an genetically modified transgenic clone and animal, for example, can be produced and can be employed to produce useful polypeptides as intended by the as-filed application. The specification provides no working examples showing a production and/or making of any transgenic animal having an intended phenotype, let alone any other phenotype as embraced by the claims. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells (Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent as to how one skilled in the art, without any undue experimentation, makes and uses any transgenic animal which must exhibit a useful phenotype, particularly on the basis of applicant's disclosure.

Note that incorporation and expression of a human truncated human PMS2 encoded construct as a foreign genetic construct into any isolated cell for recombinant production of antibodies in a cell culture, does not necessarily mean a reasonable predictability of a phenotypic expression in the founder transgenic mouse whose genome contain the transfected human truncated PMS2 encoded gene. Furthermore, there is no evidence either from the specification or from the prior art that an correct introduction via homologous recombination of a truncated human PMS2 or mouse PMS2 gene into a mouse would generate any useful polypeptide for use as a vaccine as intended by the as-filed application. Thus, it is not apparent as to how one skilled in the art know how to make and/or use any transgenic animal including a claimed gene targeted transgenic mouse as embraced by the claims without undue experimentation.

To the extent that claims 1-4, and 9-11 are readable on a method of nucleic acid therapy comprising the step of administering to any target cell *in vivo* with any of the disclosed allelic dominant negative PMS2 MMR gene, particularly in light of the specification, the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The application and claims contemplate that any nucleic acid therapy method wherein any of the disclosed allelic dominant negative MMR gene is employed would generate a systemic hypermutation in any animal so as to produce novel polypeptides that can be used as an immunognic or vaccine compositions . However, it is not apparent how one skilled in the art employs any of the disclosed allelic dominant negative PMS2 MMR gene in any gene therapy method so as to generate applicant's intended objective. The application does not provide sufficient guidance and/or factual evidence for one skilled in the art to employ any of the disclosed allelic dominant negative PMS2 MMR genes as nucleic acid therapeutic

agents, without undue experimentation. Major considerations for any nucleic acid therapy protocol involve issues that include:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA complexes to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

4/ The fraction of vector taken up by the target cell population, the trafficking of the nucleic acid within cellular organelles, the rate of degradation of the nucleic acid, the level of mRNA produced, the stability of the nucleic acid product, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced; and

4/ What amount is considered to be therapeutically effective for a nucleic acid therapy method.

In addition, all of these issues differ dramatically based on the specific carrier used, the nucleic acid being used and the disease being treated.

Apart from the problems associated with the ability to import, package, transfect, so as to release a sufficient amount of therapeutic DNA inside the cytoplasm of a target cell as indicated in the preceding paragraphs, Anderson, Nature, Vol. 392, pp. 25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). In addition, Verma *et al.*, Nature Vol. 389, pp. 239-242, 1997, states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, column 1), and that one major obstacle to success has been the ability to deliver genes efficiently by non-

viral vectors and obtain sustained expression (page 239, column 3). Even with *in vitro* cell culture trasnfected with the PMS2-134 truncated gene, Nicolaides *et al.* (Mole. Cellular Biology, Vol. 18, No. 3, p.1635-1641) teaches that (page 1640, column 2) the dominant negative attribute of the *hPMS2-134* mutant will only be manifest when it is present at sufficient concentration (at least equimolar)".

Given that *in vivo* nucleic acid therapy wherein any carrier including is employed to provide any intended effect other than simple gene expression in any and/or all mammals remains unpredictable at the tine the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any or all of the polynucleotide sequences cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention at its full breadth on the basis of applicant's disclosure.

To the extent that applicant's response (particularly pages 5-7 of the response filed 11/17/02) is applicable to the above enablement rejection, the response has been considered fully by the examiner but is not found persuasive because of the reasons set forth in the written description requirement.

Furthermore and not withstanding the lack of the written description of a representative number of species of dominant negative alleles of a *PMS2* particularly those other than a PMS2-134 truncated polynucleotide, the examiner maintains that applicant's response does not provide any evidentiary support to demonstrate that there is not undue experimentation required to practice the claimed invention as broadly claimed. Note that Note that the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

Further, the problem of predicting protein and DNA structure from sequence data of any gene and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. For example, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. See Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.). As such, the as-filed specification provides no detailed guidance whatsoever other than the essential description and/or requirement of a PMS2-134 truncated polynucleotide so as to practice the invention without any undue experimentation in regard to other transdominant negative alleles of any PMS2, let alone the issue of the lack of written description for those other than the PMS2-134 truncated polynucleotide. Birkhauser, Boston, MA, pp. 433 and 492-495). However, Applicant has provided little or no guidance beyond the given scope of the enablement and/or written description requirement. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Brenner, 1999, Trends in Genetics 15: I32; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation unnecessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use any of the claimed alleles other those described by the as-filed specification in order to practice the claimed invention as broadly claimed, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular common and/or essential structure of those claimed as dominant negative alleles of a PMS2 other than the already described PMS2-134 truncated polynucleotides, undue

experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In addition with respect to the issues of claims embracing transgenic clones and/or *in vivo* nucleic acid therapy of using an exogenous PMS2 allelic variant. Applicant mainly asserts that by claming a functional limitation of "capable of producing antibodies" and/or "antibody producer cells", the claims no longer read on transgenic clones, the assertion is not found persuasive because of insofar as the claimed invention still embraces any *in vivo* clones of cells and/or a method of making such cells in an *in vivo* environment, particularly when the claims are read in light of the as-filed specification within the context of contemplated uses, the rejection remains proper. Likewise, to the extent that the claimed method do not recite the environment where exactly the methods are employed, the claims are still read on an *in vivo* method of using an exogenous PMS2 allelic variant in any mammal so as to produce a therapeutically desired effect. Note that a simple claim amendment by reciting "*in vitro*" in the method claims and "isolated" in the claimed cells would obviate the issues of transgenic clones and/or *in vivo* gene therapy. Such claimed amendment would particularly point out applicant's invention as envisioned by applicants in the response to the previous Office action.

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed,

and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER

BACKFILE DOCUMENT INDEX SHEET

A DOCPHOENIX

APPL PARTS

_____ IMIS ____
Internal Misc. Paper

_____ LET. ____
Misc. Incoming Letter

_____ 371P ____
PCT Papers in a 371Application

_____ A... ____
Amendment Including Elections

_____ ABST ____
Abstract

_____ ADS ____
Application Data Sheet

_____ AF/D ____
Affidavit or Exhibit Received

_____ APPENDIX ____
Appendix

_____ ARTIFACT ____
Artifact

_____ BIB ____
Bib Data Sheet

_____ CLM ____
Claim

_____ COMPUTER ____
Computer Program Listing

_____ CRFL ____
All CRF Papers for Backfile

_____ DIST ____
Terminal Disclaimer Filed

_____ DRW ____
Drawings

_____ FOR ____
Foreign Reference

_____ FRPR ____
Foreign Priority Papers

_____ IDS ____
IDS Including 1449

_____ NPL ____
Non-Patent Literature

_____ OATH ____
Oath or Declaration

_____ PET. ____
Petition

_____ RETMAIL ____
Mail Returned by USPS

_____ SEQLIST ____
Sequence Listing

_____ SPEC ____
Specification

_____ SPEC NO ____
Specification Not in English

_____ TRNA ____
Transmittal New Application

_____ CTNF ____
Count Non-Final

_____ CTRS ____
Count Restriction

_____ EXIN ____
Examiner Interview

_____ M903 ____
DO/EO Acceptance

_____ M905 ____
DO/EO Missing Requirement

_____ NFDR ____
Formal Drawing Required

_____ NOA ____
Notice of Allowance

_____ PETDEC ____
Petition Decision

OUTGOING

_____ CTMS ____
Misc. Office Action

2.26.03 1449 1
Signed 1449

_____ 892 ____
892

_____ ABN ____
Abandonment

_____ APDEC ____
Board of Appeals Decision

_____ APEA ____
Examiner Answer

_____ CTAV ____
Count Advisory Action

_____ CTEQ ____
Count Ex parte Quayle

_____ CTFR ____
Count Final Rejection

INCOMING

_____ AP.B ____
Appeal Brief

_____ C.AD ____
Change of Address

_____ N/AP ____
Notice of Appeal

_____ PA.. ____
Change in Power of Attorney

_____ REM ____
Applicant Remarks in Amendment

_____ XT/ ____
Extension of Time filed separate

Internal

_____ SRNT ____
Examiner Search Notes

_____ CLMPTO ____
PTO Prepared Complete Claim Set

_____ ECBOX ____
Evidence Copy Box Identification

_____ WCLM ____
Claim Worksheet

_____ WFEE ____
Fee Worksheet

File Wrapper

_____ FWCLM ____
File Wrapper Claim

_____ IIFW ____
File Wrapper Issue Information

_____ SRFW ____
File Wrapper Search Info

REV 7/02/03